UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,917	05/21/2005	Markus Aebi	27857U	5418

20529 7590 01/23/2008

NATH & ASSOCIATES
112 South West Street
Alexandria, VA 22314

EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
01/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,917	AEBI ET AL.	
	Examiner	Art Unit	
	Iqbal H. Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-13 and 15-20* is/are pending in the application.

4a) Of the above claim(s) *5-13 and 16-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,3,4 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/4/06, 5/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-13 and 15-20 are currently pending.

This application is a 371 of PCT/CH03/00153.

The preliminary amendment filed on November 8, 2007, amending claims 1, 3-4 and 15, canceling claims 2 and 14 is acknowledged.

Election/Restriction

Applicant's election without traverse of Group I claim(s) 1-4, and 14-15, drawn to a prokaryotic organism into which is introduced a genetic information comprising a glycosyltransferase, capable of carrying out the *N*-glycosylation of the target protein, wherein said prokaryotic organism also contains the genetic information required for the expression of one or more recombinant target proteins and oligosaccharyl transferase in the communication filed on November 8, 2007 is acknowledged.

Claims 5-13 and 16-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 3-4, and 15 are under consideration and present for examination.

Priority

Acknowledgement is made of applicants claim for priority of provisional application 60/364,655 filed on 03/14/2002, and for foreign priority of Switzerland 394/02 filed on 03/07/2002.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 05/30/2006 and 05/04/2006 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are considered by the Examiner. The signed copies of IDSs are enclosed herewith.

Drawings

Drawings submitted on 09/03/2004 are accepted by the Examiner.

Specification/Informalities

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 121 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

If applicant desires priority under 35 U.S.C. 121 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as separate paragraph. The status of non-provisional parent application(s) (whether patented or abandoned) should also be included. *If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.*

Non-compliance of Sequence Rule

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that Claim 1 recites amino acid sequence of several proteins including the sequence of Asn-X-Ser(Thr) without a corresponding sequence identifier recited. See particularly 37 CFR 1.821(d).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 3-4 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites "genetic information" which is unclear as to whether the phrase encompasses DNA or RNA or both. Accordingly, claims 3-4 and 15 are rejected, as they depend on claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-4 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3-4 and 15 are directed to a prokaryotic organism E. coli into which is introduced genetic information comprising nucleic acids encoding glycosyltransferases of a type that assembles an oligosaccharide on a lipid carrier, one or more recombinant target proteins comprising sequence of Asn-X-Ser(Thr), wherein the X is any amino acid except proline, and a oligosaccharyl transferase, wherein said oligosaccharyl transferase links said oligosaccharide to said consensus sequence of said one or more a recombinant proteins.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical*).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v. G.D. Searle & Co.* the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description (see *Enzo* paraphrase above).

Thus, Claims 1, 3-4 and 15 are directed to a prokaryotic organism E. coli into which is introduced genetic information comprising nucleic acids encoding any glycosyltransferases of a type that assembles an oligosaccharide on a lipid carrier, one or more any recombinant target proteins comprising sequence of Asn-X-Ser(Thr), wherein the X is any amino acid except proline, and any oligosaccharyl transferase (OTase), wherein said oligosaccharyl transferase links said oligosaccharide to said consensus sequence of said one or more any recombinant proteins.

Claims are thus drawn to a prokaryotic organism comprising nucleic acids encoding any glycosyltransferases of a type that assembles an oligosaccharide on a lipid carrier, one or more any recombinant target proteins comprising sequence of Asn-X-Ser(Thr), wherein the X is any amino acid except proline and any oligosaccharyl transferase, wherein said oligosaccharyl transferase links said oligosaccharide to said consensus sequence of said one or more any recombinant proteins, wherein each of said proteins structures are not fully described in the specification. No information, beyond the characterization of 1) any glycosyltransferase of a type that assembles any oligosaccharide on any lipid carrier; 2) any recombinant target proteins

having consensus Asn-X-Ser(Thr), wherein the X is any amino acid except proline; and any oligosaccharyl transferase, which would indicate that applicants had possession of the claimed genus of any glycosyltransferases, any recombinant target proteins comprising sequence of Asn-X-Ser(Thr), wherein the X is any amino acid except proline and any oligosaccharyl transferase. The claimed genus of proteins encoded by the nucleic acids in said prokaryotic organism, encompass many mutants and variants. The specification does not contain any disclosure of the structure of all the recited and unknown proteins as well as mutants or variants of any glycosyltransferases, any recombinant target proteins comprising sequence of Asn-X-Ser(Thr), wherein the X is any amino acid except proline and any oligosaccharyl transferase used in making prokaryotic organism of the claim. The genus of polypeptides used in making the prokaryotic organism is a large variable genus including mutants and variants, which can have wide variety of structures. Therefore, many structurally unrelated polypeptides encoded by the nucleic acids are encompassed within the scope of the claims. The specification discloses the structure of only a single representative species of the claimed genus (glycosyltransferase from C. jejuni, AcrA target protein from C. jejuni and OTase from C. jejuni) used in making the prokaryotic organism E. coli, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 3-4 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for to a prokaryotic organism E. coli into which is introduced genetic information comprising nucleic acids encoding a glycosyltransferases from C. jejuni that transfers an oligosaccharide on a lipid carrier, a recombinant target protein AcrA comprising a consensus sequence of Asn-X-Ser(Thr), wherein the X is any amino acid except proline, from C. jejuni and an oligosaccharyl transferase (OTase) from C. jejuni, wherein said oligosaccharyl transferase links said oligosaccharide to said consensus sequence of said recombinant protein AcrA, does not reasonably provide enablement for a prokaryotic organism E. coli into which is introduced genetic information comprising nucleic acids encoding any glycosyltransferases from any source having any structural feature of a type that assembles an oligosaccharide on a lipid carrier, one or more any recombinant target proteins from any source having any structure comprising consensus sequence of Asn-X-Ser(Thr), wherein the X is any amino acid except proline and any oligosaccharyl transferase (OTase) from any source having any structural feature, wherein said oligosaccharyl transferase links said oligosaccharide to said consensus sequence of said one or more any recombinant proteins having any structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, **to make and use** the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands (858 F.2d 731,737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows:

(1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5)

the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The factors, which have, lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed below:

The breath of the claims:

Claims 1, 3-4 and 15 are so broad as to encompass a prokaryotic organism E. coli into which is introduced genetic information comprising nucleic acids encoding any glycosyltransferases from any source having any structural feature of a type that assembles an oligosaccharide on a lipid carrier, one or more any recombinant target proteins from any source having any structure comprising consensus sequence of Asn-X-Ser(Thr), wherein the X is any amino acid except proline and any oligosaccharyl transferase (OTase) from any source having any structural feature, wherein said oligosaccharyl transferase links said oligosaccharide to said consensus sequence of said one or more any recombinant proteins having any structure.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins such as any glycosyltransferase, any recombinant target proteins and any OTase protein involve in making a prokaryotic organism E. coli for producing N-glycosylated target protein including many mutants and variants broadly encompassed by the claims. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one glycosyltransferase, one target protein and one OTase protein used in making said prokaryotic organism E. coli to produce N-glycosylated ArcA protein.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art:

The amino acid sequence of a polypeptide determines its structural and functional properties. While the specification discloses a single glycosyltransferase, a single recombinant glycoprotein and a single OTase for making prokaryotic E. coli organism, neither the specification nor the art provide a correlation between structure and function such that one of skill in the art can envision the structure of any glycosyltransferase, any recombinant target proteins and any OTase protein involve in making a prokaryotic organism E. coli for producing N-glycosylated target protein in the claim. The art clearly teaches that modification of a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are tolerant of modification and which ones are conserved is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (1999) and Seffernick et al. (2001), where it is shown that even small amino acid changes result in enzymatic activity changes.

The amount of direction or guidance presented and the existence of working examples:

The specification discloses using a glycosyltransferases gene from C. jejuni that assembles an oligosaccharide on a lipid carrier, a recombinant target protein ArcA comprising sequence of Asn-X-Ser(Thr), wherein the X is any amino acid except proline from C. jejuni and an oligosaccharyl transferase (OTase) from C. jejuni, wherein said oligosaccharyl transferase links said oligosaccharide to said consensus sequence of said recombinant protein ArcA, which were introduced in a prokaryotic organism E. coli. However, the specification fails to provide any clue as to the structural elements required in any glycosyltransferase, any recombinant target proteins and any OTase protein involve in making a prokaryotic organism E. coli to be used in assembling oligosaccharide on a lipid carrier i.e. recombinant any target proteins, or which are the structural elements in said proteins to be used in making said E. coli that are essential for successfully practice the claimed invention. No correlation between structure and function has been presented.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable (Whisstock et al. 2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions.

The specification does not support the broad scope of the claims which encompass a prokaryotic organism E. coli into which is introduced genetic information comprising nucleic

acids encoding any glycosyltransferases from any source, one or more any recombinant target proteins from any source comprising consensus sequence of Asn-X-Ser(Thr), wherein the X is any amino acid except proline and any oligosaccharyl transferase (OTase) from any source because the specification does **not** establish: (A) regions of the proteins structure which may be modified without affecting said proteins activity and; (B) the general tolerance of said proteins to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any proteins amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Conclusion:

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art **to make and use** the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a prokaryotic organism E. coli into which is introduced genetic information comprising nucleic acids encoding any glycosyltransferases from any source, one or more any recombinant target proteins from any source comprising consensus sequence of Asn-X-Ser(Thr), wherein the X is any amino acid except proline and any oligosaccharyl transferase (OTase) from any source. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, making an E. coli organism by introducing said genus of genes as claimed herein is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Szymanski et al. (Mol Microbiol. 1999 Jun; 32(5):1022-30, see IDS). Instant claims are directed to an E. coli comprise any gene encoding glycosyltransferase, any gene encoding any protein comprising Asn-X-Ser(Thr) consensus sequence, wherein X is any amino acid except proline and oligosaccharyl transferase (OTase).

Szymanski et al. disclose the *pgl* gene cluster from *Campylobacter jejuni* which encodes glycosyltransferase (PglA gene) and oligosaccharide transferase (PglB) (Table 1, Fig. 1, p1024, Col 1, paragraph 1 & 2), which are the enzymes for a N-linked protein glycosylation, where said glycosyltransferase and oligosaccharide transferase enzymes sequentially add sugars to a lipid carrier that is ultimately transferred to an acceptor protein flagellin containing asparagines residues. Flagellin proteins have consensus sequence of Asn-X-Ser/Thr, wherein Asn residue is glycosylated. Szymanski et al. also disclose that *E. coli* host cells are transformed with *this pgl* gene cluster and that the resulting recombinant *E. coli* flagellin glycoprotein has changes in its glycosylation. Thus, the reference teachings anticipate the claimed invention since Szymanski et

al. teach the prokaryotic host cells containing the *pgl* gene cluster which carries out N-glycosylation of the *E. coli* flagellin glycoprotein.

Claims 1, 3-4 and 15 are rejected under 35 U.S.C. 102(a) as being anticipated by Wacker et al. (Science. 2002 Nov 29; 298(5599):1790-3, see IDS). Instant claims are directed to an E. coli comprise any gene encoding glycosyltransferase, any gene encoding any protein comprising Asn-X-Ser(Thr) consensus sequence, wherein X is any amino acid except proline and oligosaccharyl transferase (OTase).

Wacker et al. disclose the *pgl* gene cluster from *Campylobacter jejuni* which encodes glycosyltransferase (PglA gene) and oligosaccharide transferase (PglB) (Fig. 1 and 2), which are the enzymes for a N-linked protein glycosylation, where said glycosyltransferase and oligosaccharide transferase enzymes sequentially add sugars to a lipid carrier that is ultimately transferred to an acceptor protein AcrA containing asparagines residues as disclosed by the instant application. AcrA protein has consensus sequence of Asn-X-Ser/Thr, wherein Asn residue is glycosylated. Wacker et al. also disclose that *E. coli* host cells are transformed with *this pgl* gene cluster and AcrA gene, which results AcrA glycoprotein having changes in its glycosylation. The inventive entity of Wacker et al. is different from the inventive entity of the instant application (not same), which constitutes the reference by others. Thus, the invention is known or used by others. Therefore, Wacker et al. anticipate claims 1, 3-4 and 15 of the instant application.

Conclusion

Status of the claims:

Claims 1, 3-13, and 15-20 are pending.

Claims 5-13 and 16-20 are withdrawn.

Claims 1, 3-4 and 15 are rejected.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

Iqbal Chowdhury, Ph.D., Patent Examiner
Art Unit 1652 (Recombinant Enzymes)
US Patent and Trademark Office
Rm. REM 2B69, Mail Box. 2C70
Ph. (571)-272-8137, Fax. (571)-273-8137